UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/942,940	08/31/2001	Han-Mo Koo	38345-174995	8963

26694 7590 04/05/2004

VENABLE, BAETJER, HOWARD AND CIVILETTI, LLP
P.O. BOX 34385
WASHINGTON, DC 20043-9998

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/942,940	KOO ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,9,10,13-16 and 19-21* is/are pending in the application.

4a) Of the above claim(s) *6,15 and 21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-5, 7, 9-10, 13-14, 19-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

It is noted that this is not an advisory action, but rather a non-final rejection. By an inadvertent typographic mistake, the previous Office action summary of 06/05/03 indicates that it was a final rejection. However it is clear from the Office action that it was a first Office action of merit.

The following are the remaining rejections.

MISCELLANEOUS

It is noted that claims 6, 15, 21 are multiple dependent claims, and therefore are withdrawn from examination. Claims 6, 15, 21 however would be rejoined and included in the following rejections, if claims 6, 15 and 21 were properly amended.

Accordingly, claims 1, 4-5, 7, 9-10, 13-14, 16, 19-20 are being examined.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

Rejection under 35 USC 112, first paragraph of claims 1, 7, 9-10, 16 pertaining to lack of a clear written description of an organic small molecule inhbitor of MAPK/ERK kinase enzymes remains for reasons already of record in paper No.8.

Applicant argues as follows:

Applicant asserts that the claimed inhibitors have unique feature of being cytotoxic.

Applicant asserts that an additional feature that is common to the small molecule inhibitors of the present invention is that they are all noncompetitive inhibitors of MEK. Applicant asserts that in other words, they do not inhibit the binding of the enzyme to one of its substrates, adenosine triphosphate (ATP), which is the source of the phosphate group that is transferred to the other MEK substrate, the MAPK/ERK protein. Applicant asserts that moreover, some of these MEK inhibitors have been shown to share a common (or overlapping) binding site in MEK (e.g., PD098059 and U0126 as described in, Favata, M.F. et al.,"Identification of a novel inhibitor of mitogen-activated protein kinase kinasey" J Biol Chem. 1998, 273:18623-32, see, e.g., page 18623, Abstract, lines 7-9 and 13-22; page 18628, column 1, second full paragraph; page 18629, column 1, last paragraph; and page 186320, first partial paragraph).

Applicant asserts that this noncompetitive mode of inhibition of all the small molecule inhibitors described and claimed here (a fact well-known in the art, though not explicitly stated in the specification) is a common feature that sets them apart as a genus or subgenus from nearlv all other kinase inhibitors, which are ATP-competitive. See, e..g., Cohen, P., Curr Opin Chem Biol. 1999, 3:459-465 (of record in this case) at page 463, column 1, last parapaph. Thus, the compounds PD184352, PD98059 and U0126, are a rather unusual subgenus of kinase inhibitors in that they are direct, but noncompetitive, inhibitors of MEK. See, Favata, supra, and Sebolt-Leopold, J.S. et al., 1999.

The recitation of Favata, M.F. et al, Cohen, P., and Sebolt-Leopold, J.S. et al is acknowledged and entered.

Applicant's arguments set forth in paper of 12/05/03 have been considered but are not deemed to be persuasive for the following reasons:

Concerning Applicant assertion that the genus of small organic molecules have a unique function of inducing apoptosis in melanoma cells, and thereby killing melanoma cells, it is noted that a definition by function alone does not suffice to define the genus, because it is only an indication of what the genus does, rather than what it is, as taught by the Court.

The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The court stated that [a] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials. Id. At 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as vertebrate insulin cDNA or mammalian insulin cDNA without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in

> the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. At 1568, 43 USPQ2d at 1406. The court concluded that naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Id.

Concerning common feature such as being noncompetitive inhibitors of MEK, and sharing a common (or overlapping) binding site in MEK that sets them apart as a genus or subgenus from nearlv all other kinase inhibitors, which are ATP-competitive, Applicant argues limitation not in the claims.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Rejection under 35 USC 112, first paragraph of claims 1, 4-5, 7, 9-10, 13-14, 16, 19-20 pertaining to lack of enablement for a method of killing melanoma remains for reasons already of record in paper No.8.

Applicant argues as follows:

The inventors found that sustained inhibition of MAPK signaling in human melanoma cells produced by inhibiting MEK enzymatic activity, resulted in a melanoma-selective apoptotic and cytotoxic response. Applicant asserts that this provides an adequate basis for claims having the present scope. Applicant asserts that it is worth

noting again that the Sebolt-Leopold reference (of record) discloses that PD184352, by inhibiting MEK and thereby the MAP kinase pathway, resulted in a number of cellular and therapeutic outcomes, and that among them was the impairment in the growth in vivo of mouse and human colon tumors.

Applicant asserts that what the Applicants have done is to identify a different tumor type, melanoma, which not only is more reliant on MAPK activation for the properties noted above but actually depends on MAPK activation for its very survival. Applicant asserts that this leaves little room for doubt as to the effectiveness and selectivity that one of skill in the art would expect of PD184352 and the other disclosed MEK inhibitors in (a) killing melanoma cells, (b) mediating an antitumor response in a mammal, particularly a human, having melanoma, and (c) inhibiting growth, including recurrent growth, of melanoma tumor cells in a mammal.

Applicant asserts that these effects would be expected to be selective for melanoma and sparing of normal melanocytes because, as shown by the inventors, MEK inhibition does not have cytotoxic consequences on normal human melanocytes, even though it completely blocks theactivation of MAPK in these cells, arresting them in G1. However, no apoptosis was ever detected even after prolonged inhibition (specification at page 4, lines 26-29).

Applicant asserts that one of the Applicants' observations was that MEK inhibition stimulated melanin production (a normal melanocyte function) in melanoma cells thus mimicking a phenotype associated with differentiated melanocytes. Applicant asserts that cAMp-elevating agents (including both the anthrax bacillus product, “edema factor"

(EF), a protein complex, and the small molecule isobutylmethylxanthine (IBMX) are known to induce differentiation accompanied by melanin production in melanoma cells. Applicant asserts that It is important to note, however, that even though EF and IBMX synergize with MEK inhibitors in their stimulation of melanin production, both these cAMp-elevating agent dominantly antagonize the apoptosis induced by MEK inhibitors (page 4, lines 20-25; see also, Exnmple 1V). This should put to rest the concern and confusion expressed in the Office Action with regard to the existence of a correlation between "specific levels of reduction of ERK1/2 enzymes . ..but not any level of reduction" and apoptosis in vitro). There is no such thing here: MEK inhibition kills melanoma cells, and concomitant elevation of cAMp in these cells antagonizes this effect. The specification showed clearly that apoptosis in melanoma cells was not a mere "byproduct" of the differentiation induced by inhibiting MAPK signaling (e.g. page 48, lines 25-28; Figs. 5A, 5B, 6 and 8; Example IV, page 48, lines 17-18).

Applicant's arguments set forth in paper of 12/05/03 have been considered but are not deemed to be persuasive for the following reasons:

The data presented in the specification indicates that 1) there is no correlation between the inhibition of the MAPK pathway at any reduced level of ERK1/ERK2, and apoptosis in melanoma cells in vitro, and that a certain specific level of ERK1/ERK2, enzymes of the MAPK pathway seems to be required for the occurrence of apoptosis in melanoma cells in vitro.

From figure 9, and the disclosure in the specification on page 48, lines 20-23, it is clear that although IBMX alone does not reduce the level of ERK1/ERK2, and although

PD8059 alone reduces the level of ERK1/ERK2, IBMX together with PD8059 further reduces the level of ERK1/ERK2, and abolishes the apoptosis effect of PD8059 in melanoma cells in vitro. The specification specifically discloses that partial inhibition of activation of ERK1/ERK2 by PD8059 is sufficient to trigger apoptosis in melanoma cells in vitro, and that **greater degree of inhibition** of activation of ERK1/ERK2 produced by the combination of PD8059 and IBMX is not apoptotic (emphasis added).

Thus , there is no indication that there is a correlation between the inhibition of the MAPK pathway, at any reduced level of ERK1/ERK2, and apoptosis in melanoma cells in vitro, because if there is a correlation between the inhibition of the MAPK pathway at any reduced level of ERK1/ERK2, and apoptosis, one would expect that apoptosis would be enhanced in melanoma cells in the presence of both PD8059 and IBMX, in view that the level of ERK1/ERK2 is significantly reduced in the presence of both PD8059 and IBMX.

This lack of a correlation between apoptosis and the any reduced level of ERK1/ERK2, or the requirement of a specific level of ERK1/ERK2 for the occurrence of apoptosis, is further substantiated by the fact that in normal melanocytes, apoptosis does not occur in the presence of PD8059, eventhough PD8059 does reduce the level of ERK1/ERK2 in normal melanocytes cells.

Further, it is not clear how and why IBMX synergizes with PD8059 in stimulation of melanin production, nor is it clear how and why IBMX abolishes apoptosis induced by PD8059, especially in view that it is well known in the art that apoptosis is a complex

phenoma, involving several proteins, such as proteins of the Bcl family, and the proteins of the caspases family, etc...

Thus Applicant has not shown that there is a correlation between any reduced level of ERK1/ERK2 and apoptosis in melanoma cells in vitro, in view of the synergistic effect of IBMX and PD8059 on reduction of the level of ERK1/ERK2, and the abolishment by IBMX of apoptosis induced by PD8059.

It is noted that although administration of PD184352, which inhibits MEK and thereby the MAP kinase pathway, results in the impairment in the growth in vivo of mouse and human colon tumors, this cannot apply to melanoma cells, because different cancer cells have different etiology and characteristics, and one cannot predict that melanoma cells would react the same way to PD184352 in vivo.

Thus, in view that only a certain specific level of reduction of ERK1/2 , enzymes of the MAPK pathway, but not any level of reduction of ERK1/2, seems to be correlated with apoptosis in melanoma cells in vitro, and because of possible homeostasis regulation, which is a common phenomena in vivo, one cannot predict that PD184352 would reduce ERK1/2 , enzymes of the MAPK pathway, to a specific level in melanoma cells *in vivo*, effective for inducing apoptosis of human melanoma cells in vivo. Further, cancer cells in vitro have different properties and characteristics than primary cancer cells, as taught by Drexler et al, Embleton et al, Hsu et al, Freshney et al, and Dermer, all of record, and thus it is unpredictable that cancer cells in vitro would have the same responses to drugs as primary cancer cells.

Moreover, one cannot extrapolate the in vitro teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, as taught by Gura, Jain, Curti, and Hartwell et al, all of record.

For the reasons set forth above, and in previous Office action, one cannot predict that the claimed method would be effective in killing melanoma cells in vivo.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, YVONNE EYLER can be reached on 571-272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

March 29, 2004